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The goals of this research are to develop interdisciplinary studies of the etiology, biology and prevention of ovarian cancer. **Project I, Ovarian Cancer Consortium** has registered 293 participants including 97 ovarian cancer patients representing 165 families. The Core Laboratory has collected, processed and banked biospecimens from 235 subjects. **Project II, Facilitating Decision Marking About Prophylactic Oophorectomy**: baseline data on 68 women are available for preliminary analysis; 10 women, (14.7%) made a decision about having prophylactic oophorectomy while 53 women (77.9%) have not made a decision, and 5 women (7.4%) did not answer the questionnaire. Five of the 10 women who made a decision have gone on to have prophylactic oophorectomy. **Project III, Phase II Chemoprevention Study of Ovarian Cancer**: this placebo-controlled randomized protocol using 4HPR has been written, approved by the Dept. of Defense, the National Cancer Institute Chemoprevention Branch, and the FDA. It has been offered to the Gynecologic Oncology Group for implementation throughout the country by interested gynecologists. Data entry and quality control systems have been established and 14 different case report forms are finalized. To data, four women have signed consent forms, three were enrolled in the Ovarian Tissue Donation Portion of the study, and one has randomized to treatment and completed her prophylactic oophorectomy in March 2000.

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# Table of Contents

# ANNUAL REPORT – YEAR TWO

## PROJECT I

## OVARIAN CANCER CONSORTIUM FOR RESEARCH AND SURVEILLANCE (OCCRS)


| | | |
|---|---|---|
| **Project Director** | **Mary B. Daly, M.D., Ph.D.** | **Fox Chase Cancer Center** |
| **Co-Investigator** | **Andrew K. Godwin, Ph.D.** | **Fox Chase Cancer Center** |
| **Statistician** | **Andre Rogatko, Ph.D.** | **Fox Chase Cancer Center** |

## INTRODUCTION

Ovarian cancer continues to be the leading cause of death from a gynecologic malignancy among women in the United States. While a significant impact on this sobering reality has not yet been realized, the community affected by the disease has raised its collective voice to promote awareness and patient advocacy. The OCCRS, now in operation at Fox Chase Cancer Center (FCCC) for two years, has experienced a strong, steady base of recruitment due in part to the ovarian cancer community's motivation to aid research. Networking with local and national advocacy organizations has yielded an enrollment of 293 patients and family members representing 32 states and Canada. The work of this family registry has been further expanded by our three collaborating sites, Reading Medical Center in Reading, PA, Cooper Medical Center in Camden, NJ, and Wake Forest University Baptist Medical Center in Winston-Salem, NC, which are actively recruiting participants. Our staff remains inspired by the families' high level of compliance in completing questionnaires and donating blood and tumor tissue samples. Information obtained is maintained in a sophisticated relational database system. Laboratory research is underway using DNA from registry samples under the direction of Dr. Andrew Godwin to identify and characterize common genetic polymorphisms in genes involved in steroid hormone metabolism. The scope of the OCCRS encompasses a research-based infrastructure to facilitate the conduct of translational research, to promote rapid communication of relevant findings to the professional and lay communities, and to transfer novel prevention, screening and treatment strategies into clinical practice.

## BODY

The operational premise for expanding the OCCRS in Year Two was to fully establish procedures and begin active recruitment at the collaborative institutions. The following is a description of the research accomplishments associated with each Task as outlined in the approved Statement of Work.

### Task 1. Development and Implementation of a Recruitment Strategy – Months 1-6

Key personnel are actively involved at each site **(See Appendix A)**. Site visits have been made by the Project Manager to review policies and procedures and to train staff in recruitment of eligible participants. Marketing of the study has been creatively adapted to the unique patient and high-risk populations in each geographic area:

***Reading Medical Center:*** The Family Risk Assessment Program (FRAP) Coordinator has networked with key gynecological and medical oncology physicians and nurses to discuss the study and provide informational brochures to patients. Ads have been run in newspaper and institutional newsletters. Two women have been recruited through the FRAP program, having received education, cancer risk counseling and complied with study requirements after informed consent.

***Wake Forest University Baptist Medical Center:*** Research fellows have been hired and have fully established operating procedures. Recruitment strategies include accessing a large Ovarian Cancer Screening Study database, Tumor Registry patients and networking with local physicians and support groups. Campus-wide newsletter articles and participation in community

awareness programs are key to the marketing plan. To date 14 blood samples have been forwarded to Fox Chase Cancer Center.

***Cooper Medical Center:*** A Genetic Research Coordinator has been hired and oriented to OCCRS procedures. Recruitment strategies have been targeted through gynecologic-oncology staff and through the Cancer Risk Evaluation Center. Potential participants are being contacted personally and by letter.

**Total Participation from all sites (including FCCC):**

To date, 293 participants, including 97 ovarian cancer patients and representing 165 families are enrolled. One hundred forty-nine (149) families had one case of ovarian cancer, 25 had two cases and 10 had more than two. Ninety (90) families had both breast and ovarian cancer, supporting the clustering of these cancers in women with BRCA1 and BRCA2 mutations. In support of these observations, 1 BRCA1 mutation was detected in 9 of the participants which were randomly selected and 6 mutations were uncovered in 24 women of Ashkenazi Jewish heritage. The median age of OCCRS participants is 47 years, with a range of 16 to 89 years. The geographic base of recruitment has increased significantly due to networking with national advocacy organizations such that women in 32 states and Canada are enrolled.

**Task 2. Establishment of a Computerized Data Base – Months 1-6**

A relational database system has been developed to maintain all of the information obtained in this research. Included in this information system is health history, family history, clinical, epidemiologic, socio-demographic, psychosocial and laboratory data. In addition, this database contains cancer and vital status data on relatives of individuals recruited into the study. This database software system coordinates numerous tasks including the scheduling of follow-up visits, the distribution of mailed self-report questionnaires and the generation of contact logs for conducting telephone interviews. This system is capable of generating multigenerational pedigrees from the union of family histories provided by two or more distinct study subjects in the same family. The family data is easily updated from follow-up information to include deaths or new cancers reported for study subjects, previously listed family members, as well as new births. Screens have been developed to log in blood samples received from collaborating sites and generate reports for reimbursement.

**Task 3. Development of Informed Consent Practice – months 1-4**

The goal of our consent process is to provide participants a full understanding of the proposed research and its potential risks and benefits in order to ensure informed decisions. Consent is obtained in a multi-staged process, first over the phone and later via established consent forms of which annual IRB review and approval took place 9/14/2000. Separate consent forms for the Symptom Checklist substudy were developed and approved by the Research Review and Institutional Review Board Committees on 2/22/2000 and revised for address change on 4/12/2000. **(See Appendix B)**

**Task 4. Establish an Ovarian Cancer Tissue Bank – Months 1-36**

Biospecimen collection is actively underway at all sites except Cooper Medical Center, where potential participants are now being identified. Well-established protocols for collecting blood and tissue specimens are in use and all staff are trained. Blood specimens from the Wake Forest site are being collected in the General Clinical Research Center (GCRC), where staff are highly skilled in preparing research protocol specimens.

To date, 41 sets of tumor tissue blocks and/or slides have been released to FCCC from various pathology departments in hospitals where OCCRS participants had surgery.

**Task 5. Development and Implementation of Symptom Checklist**

We are actively interviewing ovarian cancer patients who have been diagnosed within the last two years to learn of their physical experiences prior to diagnosis. Our initial intention was to perform these interviews in a focus group format but we've changed to an individual interview process due to scheduling conflicts among the participants. All interviews begin with informed consent and are audiotaped. We are networking with a local ovarian cancer advocacy organization to access more patients to meet our goal of 50 interviews.

**Task 6. Standardization of Genetic Risk Counseling Protocols – Months 1-6**

The comprehensive genetic risk counseling protocol developed in the Margaret Dyson Family Risk Assessment Program at FCCC is the model for the programs at the Reading Medical and Cooper Medical Centers. The Wake Forest site collaborates with a certified genetic counselor to provide risk counseling.

**Task 7. Develop a Comprehensive Education Program for Providers and Participants - Months 1-36**

We continue to utilize a well-developed slide presentation as well as a sophisticated compact disc-interactive (CD-i) format for educational purposes. The CD-i is currently being converted to CD-ROM format. As of April 2000 a new publication, *Resources – A Guide For Women living With Ovarian Cancer,* became available and has been used for the patients in our program. The lead author of the guide is Virginia R. Martin, RN, MSN, AOCN, Clinical Director of Ambulatory Care at FCCC; we work closely with Ms. Martin to identify ovarian cancer patients for OCCRS participation and for assisting patients with care issues. The Project Manager has collected gynecologic cancer educational brochures in Spanish and in the coming year we will work with the staff at Cooper Medical Center to evaluate and implement these resources as needed.

The FCCC website, http://www.fccc.edu has been recently updated and contains a wealth of information about ovarian cancer and current research studies and findings.

An insert to the Family Risk Assessment Program's newsletter, *Prevention Matters*, focusing specifically on our ovarian cancer research, has recently been printed. This piece was approved by our IRB as a recruitment tool and we have distributed it at local and national ovarian cancer advocacy events. **(See Appendix C)**

Plans are underway for a display of ovarian cancer awareness quilts in our Cancer Prevention Pavilion in October 2000 to raise awareness of prevention research.

## KEY RESEARCH ACCOMPLISHMENTS

- Two hundred-ninety three (293) participants, including 97 ovarian cancer patients and representing 165 families have been recruited into the OCCRS. In support of the OCCRS, the Core Laboratory has collected, processed and banked biospecimens (e.g., serum, platelets, DNA, and lymphocytes) from 235 blood samples.
- The DNA from blood and ovarian tumors distributed to multiple investigators for various studies outlined in Dr. Andrew Godwin's Laboratory Core portion of this annual report includes a subset of OCCRS participants.
- A limited number of OCCRS participants have been tested for germline mutations in BRCA1 and/or BRCA2. Six (6) BRCA1 and one (1) BRCA2 mutations have been detected in just 16 of the participants which were randomly selected and six (6) mutations (five in BRCA1 and one in BRCA2) were uncovered in 24 women of Ashkenazi Jewish heritage. Further studies by Dr. Andrew Godwin's group are scheduled to determine the prevalences of germline BRCA1 and BRCA2 mutations in population-based samples of ovarian cancer cases in the U.S. and Canada.
- Laboratory research is underway using DNA from the OCCRS to:
  a) identify novel genetic polymorphisms in the human arylsulfatase gene from 100 samples: a SNP in the 3' – flanking region has been identified.
  b) identify common alleles in the human UDP-glucuronosyltransferase gene, UGT1A6. Thus far four common alleles have been identified and will be further characterized for functional significance with funding from a DOD Breast Award.
  c) identify novel genetic polymorphisms in the human sulfotransferase gene, SULT2B1; this project is in the beginning stages.
  d) determine is LOT-1 on chromosome 6q is maternally imprinted and if loss of the paternal allele is involved in ovarian carcinogenesis.

## REPORTABLE OUTCOMES

### Abstracts

SCREENING FOR OVARIAN CANCER: DETERMINANTS OF ADOPTION BY HIGH RISK WOMEN. Daly, Mary, Zojwalla, Naseem, Cherry, Carol, Malick, John. Fox Chase Cancer Center.

This abstract, prepared for the Third Biennial Ovarian Cancer Research Symposium in Seattle, Washington, September 15-16, 2000 presented by the Marsha Rivkin Center for Ovarian Cancer Research, incorporated data gathered in part from OCCRS participants.

### Development of Cell Lines

Primary cell lines were generated from the ovaries of eight (8) BRCA1 and BRCA2 mutation carriers as well as control individuals. These cell cultures are being used in a collaborative study with Dr. A. Knudson (Senior Member, FCCC) entitled "Evaluation of *in vivo*

and *in vitro* pharmacology and toxicology of preventative agents using human mutant cells from dominantly heritable cancers" to study the changes in gene expression following treatment with a variety of chemoprevention agents in culture.

Three (3) primary human ovarian surface epithelial (HOSE) cell cultures and three (3) mortal, SV40 expression and three (3) matching immortal SV40 expressing HOSE cell lines were given to Drs. P.Engstrom (P.I.) and C. Patriotis (Associate Member, FCCC) for evaluation of changes in gene expression patterns following 4-HPR treatment.

## CONCLUSIONS

Recruitment into the OCCRS has increased steadily during the past year due in part to the energy of the ovarian cancer advocacy community. While our numbers do not meet those originally anticipated we find a high rate of compliance to complete all study requirements, (i.e., numerous data collection tools, blood sampling, tissue donation and permitting access to extended family members for recruitment) on the part of those who participate.

Barriers to meeting goals include the extended time frame needed to get the collaborative sites up and running. It took a full year from the initial site visit to Wake Forest University Baptist Medical Center to hire and train study coordinators, adapt procedures and obtain IRB and GCRC approvals. Cooper Medical Center's process has been hampered by the multiple responsibilities of key project staff who are new in the last year. It should also be noted that while most potential participants we have contacted have expressed interest, 20 women declined due to recurrent disease or elderly/infirm status and six (6) have been noncompliant with completion of data.

Key research accomplishments as outlined earlier indicate that important studies are underway to provide important insight into molecular genetic mechanisms associated with ovarian epithelial oncogenesis. We anticipate ongoing active recruitment to build this valuable resource to support future research.

# ANNUAL REPORT – YEAR TWO

## PROJECT II

## FACILITATING DECISION MAKING ABOUT PROPHYLACTIC OOPHORECTOMY


| | | |
|---|---|---|
| **Project Director** | **Dr. Suzanne M. Miller** | **Fox Chase Cancer Center** |
| **Co-Investigator** | **Dr. Carolyn Y. Fang** | **Fox Chase Cancer Center** |

## INTRODUCTION

Project II, *Facilitating Decision-Making about Prophylactic Oophorectomy,* focuses on how women with a familial risk of ovarian cancer make decisions regarding their preventative options, specifically prophylactic oophorectomy (surgical removal of healthy ovaries). The primary goal of the study is to explore the psychological factors that influence a woman's decision to undergo or forego the procedure. A secondary goal is to identify whether high monitors (who typically scan for and exaggerate cancer threats) show a different pattern of response than low monitors (who typically distract from and minimize health threats). Data obtained from this study will be used to develop an enhanced counseling intervention to facilitate decision-making and maximize patient adjustment. A pilot study will be designed and conducted to provide a preliminary evaluation of the feasibility and efficacy of an enhanced counseling intervention.

## BODY

A procedural plan was designed to ensure consistency in dealing with multiple sites. This entails identifying key personnel, developing a standardized protocol to contact potential participants, and the establishment of a computerized database for all study data. A series of meetings held between staff at FCCC and contacts at collaborating sites enabled us to systematically develop and enact this plan. The study is being conducted at Fox Chase Cancer Center, as well as at satellite sites including Cooper Health System, Reading Hospital, and Graduate Hospital. Four evaluation time-points include a baseline assessment with 3-, 6-, and 12-month follow-up assessments. Measures include background variables (i.e., demographics, personal health history, medical status), person variables (i.e., attentional style), process variables (i.e., the patient's level of perceived risk, perceived control, distress, values/goals, and self-regulatory coping strategies), and outcome variables (i.e., decision-making regarding prophylactic oophorectomy. Data obtained from this study will be used to develop an enhanced counseling intervention to facilitate decision-making and maximize patient adjustment. The Cognitive-Affective Processing (CAP) intervention will be designed to enable the prophylactic oophorectomy candidate to realistically anticipate scenarios that might develop, thereby providing a more informed basis for making her surgery decision and dealing with its consequences. A pilot study will be designed and conducted to provide a preliminary evaluation of the feasibility and efficacy of the CAP intervention.

At the time of this report, 58.8% (97/165) of women contacted via telephone have given verbal consent to participate in the study. Seventy-eight-percent (76/97) of the women who gave verbal consent returned their written consent form and baseline packet of questionnaires. Eighty-four-percent (46/55) of the women eligible to receive their 3-month assessment have returned their packet, while we are still waiting for 16% (9/55) of the distributed packets to be returned. Seventy-seven-percent (23/30) of the women eligible to receive their 6-month assessments have returned their packet, while we are still waiting for 23% (7/30) of the distributed packets to be returned. Twenty-five percent (1/4) of the women eligible to receive their 12-month assessments have returned their packet, while we are still waiting for 75% (3/4) of the distributed packets to be returned.

## KEY RESEARCH ACCOMPLISHMENTS

- Implementation of study protocol, initiation of recruitment efforts, and analysis of baseline data.

- A review and analysis of the literature on decision-making about prophylactic oophorectomy was conducted. This review paper, *Decision Making about Prophylactic Oophorectomy among At-Risk Women: Psychological Influences and Implications,* has been published in Gynecologic Oncology (Miller, Fang, et al., 1999).

- Completion of pilot studies investigating the predictors of women's intentions to undergo prophylactic oophorectomy. An empirical paper entitled *Anxiety/Uncertainty Reduction as a Motivation for Interest in Prophylactic Oophorectomy in Women with a Family History of Ovarian Cancer* has been submitted to the Journal of Women's Health (Hurley, Miller, et al.). This study investigated the relation of cancer anxiety and other factors to interest in prophylactic oophorectomy in a group of women with varying degrees of familial risk for ovarian cancer. Another empirical paper, *The Influence of Attentional Style and Risk Perceptions on Intentions to Undergo Prophylactic Oophorectomy Among FDRs,* is under review at Psychology and Health (Fang, Miller, et al.). This paper illustrates the impact of monitoring attentional style and perceived risk on at-risk women's intentions to undergo prophylactic oophorectomy.

## REPORTABLE OUTCOMES

To date, all of the women who have agreed to participate in this study are Caucasian. Approximately 83% of the women have at least a college degree, and 16% have completed a high school degree. The majority (76.8%) of the women are currently married. Sixty-nine-percent are currently employed. The mean age of the participants is 40 years old.

At the time of this progress report, baseline data for 68 women were available for preliminary analysis. The analysis indicated that ten women (14.7%) had made a decision about having a prophylactic oophorectomy, while 53 women (77.9%) had not made a decision and 5 women (7.4%) did not answer the question. Of the 10 women who had made a decision about having a prophylactic oophorectomy, 5 (50%) of the women have had the surgery and 5 (50%) have not had the surgery. Of the 5 women who have made their decision, but have not had surgery, 2 women were definitely not going to have the surgery. The remaining 3 had made their decision to not have surgery at the present time, but 2 of those 3 women reported that they were likely to have the surgery someday.

Of the 53 women who were still in the decision-making process, 17 women (32%) were quite a bit (24.5%) or definitely (7.5%) interested in learning more about prophylactic oophorectomy. Thirteen women (24.5%) stated that it was quite a bit (15.1%) or definitely (9.4%) likely that someday they would have a prophylactic oophorectomy.

As in previous studies, high monitors felt at greater risk for developing ovarian cancer. High monitors were more likely to report that their chances of getting ovarian cancer someday were greater than women their own age ($r$=.32; $p$<.05). In addition, monitors were more likely to rate

their chances of getting ovarian cancer someday (on a 0-100% scale) to be high ($r$=.33; $p$<.05). The analysis also revealed an interesting relationship between monitoring and interest in prophylactic oophorectomy. Among women who were still in the decision-making process, high monitoring was associated with greater interest in having a prophylactic oophorectomy within the next 6-months ($r$=.34; $p$<.05). However, among women who had made their decision about surgery, there was a trend suggesting that high monitors (as determined by a median split) were actually less likely to have had the surgery ($X^2 = 2.67$, $p = .10$).

## CONCLUSION

This research will fill a void in the ovarian cancer risk literature. Women with an increased risk of ovarian cancer face a difficult decision regarding preventative surgery, and few resources are available to help them with their decision. Hence, it is important to explore factors associated with decision-making and to use the information to develop effective counseling interventions. Through more systematic investigation of these factors, we will be able to develop a profile of decision making that will be used to design an enhanced counseling intervention. A pilot study will then investigate the effectiveness of the resulting counseling intervention.

## REFERENCES

Miller, S. M., Fang, C. Y., Manne, S. L., Engstrom, P. F., & Daly, M. B. Decision making about prophylactic oophorectomy among at-risk women: Psychological influences and implications. *Gynecologic Oncology, 75*, 406-412, 1999.

Hurley, K. E., Miller, S. M., Costalas, J. W., Gillespie, D., & Daly, M. B. Anxiety/Uncertainty Reduction as a Motivation for Interest in Prophylactic Oophorectomy in Women with a Family History of Ovarian Cancer. Submitted.

Fang, C. Y., Miller, S. M., Daly, M. B., & Hurley, K. The influence of coping style and risk perceptions on decisions to undergo prophylactic oophorectomy among FDRs. Submitted.

# ANNUAL REPORT – YEAR TWO

## PROJECT III

## PHASE II CHEMOPREVENTION STUDY OF OVARIAN CANCER

**Project Director** **Robert F. Ozols, M.D., PH.D.** **Fox Chase Cancer Center**

## INTRODUCTION

Fenretinide, a retinamide derivative of vitamin A, is a promising chemopreventive agent, which induces apoptosis and decreases cell proliferation. It has an inhibitory effect on the growth of ovarian cancer cells and surface epithelial cells of the ovary. This research study tests the hypothesis that treatment of high-risk individuals with fenretinide will change the histologic features associated with a preneoplastic phenotype in ovaries as well as alter putative biomarkers of preneoplasia. To test our hypothesis we are conducting a Phase II clinical trial of fenretinide versus a placebo in women with high risk of developing ovarian cancer and a desire to undergo oophorectomy for prophylaxis. At the completion of the treatment phase of the clinical trial, all patients will undergo oophorectomy, and the histologic characteristics of the ovaries from the two groups of patients will be compared as well as markers of cell proliferation and apoptosis. In addition, these results will be compared to ovaries removed from untreated individuals at no increased risk for ovarian cancer. This study will establish baseline values of SEBs in high-risk and normal-risk populations as well as evaluate the specific effect of fenretinide treatment on cell proliferation and apoptosis in precursor lesions of an ovarian cancer-prone population.

## BODY

A total of 71 participants (including a 10% "drop-out" rate) will be randomized to allow 32 evaluable participants per arm. Eligible to participate are women greater than 18 years of age who have decided to undergo a prophylactic oophorectomy due to increased risk for ovarian cancer defined by: 1) evidence of a genetic defect in BRCA1 or BRCA2, or 2) one or more first-degree relatives diagnosed with ovarian cancer prior to the age of 50 years, or 3) other family history contributing to risk: one first-degree relative diagnosed with ovarian cancer at any age and at least one other first- or second-degree relative diagnosed with ovarian cancer at any age.

Participants are randomized to take daily oral doses of either 400 mg 4-HPR or placebo for 4-6 months with monthly 3-day drug holidays. Following this treatment period, the participant undergoes the planned prophylactic oophorectomy 7-10 days after the first day of her menstrual cycle. The primary objectives are to assess the effect of 4-HPR on ovarian histology; and the effect of 4-HPR on potential surrogate endpoint biomarkers (SEBs): apoptosis (TUNEL and immunohistochemistry of single-stranded DNA), apoptosis (regulation (bcl-2 and Bax expression), and one marker of proliferation (MIB-1 protein level). Additional control ovarian tissue will be obtained from: 1) high-risk individuals who are eligible for the trial but uncomfortable waiting 4-6 months for their oophorectomy, and 2) normal, low-risk individuals. These banked tissue samples will assist in evaluating the variability between individuals over time and the significance of SEBs for ovarian cancer. The total duration of the study is three years.

In May 1998, the Department of Defense notified the FCCC of its recommendation to fund our clinical prevention trial "Evaluation of Fenretinide as a Chemopreventive Agent for Ovarian Cancer." The study was submitted to the FCCC Research Review Committee (RRC) in June 1998. This committee reviews proposed clinical studies from the perspective of scientific rationale, study design, feasibility and conduct, patient registration and data management, statistical appropriateness and institutional priority. Additional information and revisions were

requested by the RRC. Following institution of these changes, the study was approved by the RRC and submitted to the Institutional Review Board (IRB).

In August 1998, this IRB-approved clinical trial was reviewed by the Surgeon General's Human Subjects Research Review Board (HSRRB). Additional clarifications were requested and instituted. Approval was granted.

In February 1999, this study underwent review by the National Cancer Institute, Chemoprevention Branch (NCI, CB). The NCI, CB is very supportive of this study and is providing fenretinide as well as placebo. The NCI has certain responsibilities as Sponsor for the Investigational New Drug application (IND) of fenretinide. In order for the NCI, CB to fulfill its responsibilities, the protocol, associated case report forms, and consent were revised for submission to the Federal Drug Administration (FDA) as part of the fenretinide IND application.

In June 1999, this study underwent review and approval by the FDA as part of the fenretinide IND application. In late June 1999, FCCC received fenretinide and placebo from the NCI.

The research protocol review and approval process was complicated and lengthy. As summarized in Table 1, 31 women have been recruited to the study. To date, 4 women have been evaluable per the protocol. Three individuals were enrolled to the ovarian tissue donation portion of the study and have already donated ovarian tissue at the time of their surgery. One woman was randomized to fenretinide or placebo for four months prior to her prophylactic oophorectomy, which was performed in March of 2000.

Recruitment through the family risk assessment program at FCCC continues. Genetic counselors at academic institutions in Pennsylvania have been contacted and given study information to provide to eligible women they may be counseling.

The Gynecologic Oncology Group plans to implement this important study through their cooperative group mechanism. This would not only assist in accrual of this limited population but will make this scientifically interesting study available to high-risk women around the country.

## KEY ANTICIPATED RESEARCH ACCOMPLISHMENTS

Anticipated key research accomplishments emanating from this research include the following:

- Success in altering the SEBs in this clinical trial format would justify prolonged treatment with fenretinide and provide an alternative to oophorectomy for prophylaxis in women at high risk for ovarian cancer.

- Tissues obtained during this research will be a resource for further studies of molecular carcinogenesis in ovarian cancer. This effort may lead to the identification of specific novel targets for therapy and prevention in patients with hereditary ovarian cancer and the more common sporadic epithelial ovarian cancer.

## REPORTABLE OUTCOMES

The research protocol review and approval process was complicated and lengthy. Thus, no individuals have been enrolled to date. However, during this process, data collection and management systems were created in preparation for study activation.

1. Data Entry, Management and Quality Control

The large volume of information to be generated in this project requires the implementation of computer-based tools for the management and coordination of data. The Population Informatics Facility (PIF) is responsible for all database and statistical programming aspects of this study. The purpose of the PIF is to provide Informatics expertise to facilitate the research conducted by investigators at FCCC. PIF personnel designed and developed the appropriate database, created the data entry interface, trained the technicians in its use, and provided regular feedback on data quality.

At recruitment, each subject will be given a unique identification number. Baseline information on health, family and dietary history, along with pretreatment laboratory and clinical test results will be entered onto prepared hardcopy (paper) data collection instruments by a study representative. Upon completion, these forms will be sent to the FCCC Chemoprevention Protocol Office (CPO) where the data will be entered via terminals into the database using the electronic data system created by PIF programmers.

At each subsequent follow-up contact, a study representative will complete hardcopy questionnaires containing information on study subject compliance with pill consumption, toxicity symptoms, results of routine blood sample analyses, and clinical observations made by the attending physician. Similarly, the study representative will place results from all laboratory procedures on hardcopy data collection instruments. These forms will be sent to the Protocol Coordinator for data entry. All laboratory records will include the unique identifier and date of collection of the biologic sample.

The information system for this project was built on the system that has been developed by PIF to support the Chemoprevention Clinical Trials at FCCC. As of May 1, 1999, the Chemoprevention Clinical Trials database stores information on 1,526 study subjects from seven chemoprevention trials at FCCC. This DBMS maintains all of the data collected in these studies and is designed to facilitate many aspects of data collection and patient tracking. Based upon the data entered into the database, this software system is capable of performing such tasks as the determination of study eligibility, automated subject randomization and the generation of mailed reminder letters. Most, if not all, of these capabilities have been incorporated into the systems developed for this project.

The existing database management system uses the relational database product ORACLE as the primary software platform for data entry and validation, storage, retrieval, modification, and security. This software system runs on a UNIX-based distributed computing system. These computers are maintained by the Research Computer Services facility at the Fox Chase Cancer Center. This distributed computing system is an integral part of a Local Area Network (LAN) which provides connections to a Digital VAX computer, IBM compatible PC's, Macintoshes,

printers, plotters, and the Internet. The software developed to meet the needs of this study will also use these computing facilities.

On-screen data entry forms, designed to resemble the data collection instruments, will be created using the ORACLE Forms V6.0 software. Data validation will occur both during and after data entry. Range, validity and logical consistency checks will be conducted during the data entry process to ensure data quality. Reports generated from the entered data will be compared to the original data collection instruments to further ensure the accuracy of the data stored on magnetic media. Edits will be conducted using the query-by-form capability of ORACLE. This system of data entry and corrections will allow the data analyst to have access to the most up-to-date and accurate data at any given time. Daily backups of the database will be conducted to protect against accidental corruption or deletion of the data. Statistical computing will be performed using a variety of statistical packages including SAS, BMDP, IMSL, Splus and other custom written programs.

In order to preserve privacy and confidentiality, a series of security measures will be undertaken. Only the person-specific identifier, and date of collection when appropriate, will be stored with study results. Lists of Ids matched with names and addresses will be stored by the investigators in locked filing cabinets. Further, through the use of the security measures available within the operating system (UNIX) and the relational database management software (ORACLE), restrictions will be applied to each user commensurate with their needs to access the data. All new personnel with any access to the data will be trained in the ethics of electronic data access.

2. Case Reports Forms

Data from these studies will be kept in a database consisting of 14 data "tables": (1) Initial Contact/On-study; (2) Eligibility Checklist; (3) Health History Data; (4) Baseline Epidemiologic Data (e.g., smoking and alcohol intake, reproductive history, weight, etc.); (5) Concomitant Medications; (6) Diet Data; (7) Pretreatment signs and Symptoms; (8) Physical Examination; (9) Study Drug Administration; (10) Compliance Measures; (11) Toxicities; (12) Routine Laboratory Studies (e.g., CBC, electrolytes, liver function tests, etc.); (13) Research studies (Mib-1, apoptosis markers, etc.); and (14) Off-study. Some of these tables will have one record per subjects (e.g., Health History Data) while other may have multiple records per subject (e.g., Toxicities), each identified by the individual-specific identification number and date of collection. All tables can be linked by their unique individual identification number (and date of collection, when appropriate).

3. Publications/Presentations

Robert F. Ozols, M.D., Ph.D. presented this study at the Helene Harris Memorial Trust Forum on Ovarian Cancer in Stockholm, Sweden in April 1999. Proceedings are being published in book form as part of the "Ovarian Cancer" series.

## CONCLUSIONS

The clinical trial is ongoing; thus, no conclusions can be made at this time.

## A Phase II Evaluation of Fenretinide (4-HPR) as a Chemopreventive Agent for Ovarian Carcinoma
## RECRUITMENT

| Study # | Screening Date | Referral | Eligible Yes/No | Enrolled Yes/No | Reason Not Enrolled | Date Of Consent | Arm: D=drug vs. T=tissue only |
|---|---|---|---|---|---|---|---|
| 6001 | 08/16/99 | FRAP | Y | Y | - | 10/29/99 | D |
| 6002 | 07/20/99 | FRAP | Y | Y | - | 11/18/99 | T* |
| 6003 | 08/02/99 | FRAP | Y | Y | - | 02/09/00 | T** |
| 6004 | 08/02/99 | FRAP | Y | N | Undecided- seeking 2nd opinion | - | - |
| 6005 | 08/02/99 | FRAP | Y | N | Undecided | - | - |
| 6006 | 08/02/99 | FRAP | Y | N | Undecided | - | - |
| 6007 | 08/02/99 | Boente | Y | N | Had 2nd ovary removed in 3/99 | - | - |
| 6008 | 08/08/99 | FRAP | ? | N | No response from participant | - | - |
| 6009 | 08/09/99 | FRAP | Y | N | Emergency oophorectomy -9/99 | - | - |
| 6010 | 08/22/99 | Internet | Y | N | undecided | - | - |
| 6011 | 10/26/99 | FRAP | N | N | Surgery not recommended by MD | - | - |
| 6012 | 11/18/99 | Internet | N | N | Currently being treated for breast ca | - | - |
| 6013 | 01/03/00 | Friend/FOCUS | N | N | Surgery scheduled- 01/10/00 | - | - |
| 6014 | 01/04/00 | FOCUS | N | N | Has not spoken to MD/Gyn nor undergone counseling | - | - |
| 6015 | 01/04/00 | FOCUS | N | N | Currently being treated for breast ca and has not received genetic counseling. | - | - |
| 6016 | 01/06/00 | Unknown | N | N | Gyn doesn't agree with surgery nor has patient undergone counseling. | - | - |
| 6017 | 01/31/00 | Boente | N | N | Has not undergone genetic counseling | - | - |
| 6018 | 01/10/00 | FOCUS | N | N | Has not undergone genetic counseling | - | - |
| 6019 | 03/01/00 | Internet | N | N | Did not meet criteria- cystic disease | - | - |

*could not d/c NSAID

** taking oral contraceptives for ovarian cysts

| Study # | Screening Date | Referral | Eligible Yes/No | Enrolled Yes/No | Reason Not Enrolled | Date Of Consent | Arm: D=drug vs. T=tissue only |
|---|---|---|---|---|---|---|---|
| 6020 | 03/03/00 | FRAP | Y | Y | Currently taking Prempro. Colonscopy scheduled 3/22/00 for + quaiac. Will call when ready for surgery. | | |
| 6021 | 03/03/00 | FRAP | Y | Y | Undecided bewteen ooph or hyster. OV with Daly on 4/28 to make final decision. Possibly tissue only. | | |
| 6022 | 03/29/00 | FRAP | Y | N | Undecided | | |
| 6023 | 05/10/00 | FRAP | Y | Y | - | 05/23/00 | T |
| 6024 | 03/23/00 | FCCC-Website | N | N | Has not undergone genetic counseling | - | - |
| 6025 | 05/05/00 | Bergman clinic | Y | Y | Undecided- may postpone surgery for years | - | - |
| 6026 | 05/19/00 | Bergman clinic | Y | Y | Undecided | - | - |
| 6027 | 05/04/00 | Bergman clinic | N | - | Has not undergone genetic counseling | - | - |
| 6028 | 06/28/00 | FRAP | ? | N | Diagnosed with (?) ovarian cancer prior to decision with M.D. for surgery | - | - |
| 6029 | 05/30/00 | Email through Ozols | ? | ? | May postpone surgery until menopause | - | - |
| 6030 | 07/19/00 | Bergman clinic | ? | N | Has not undergone genetic counseling | - | - |
| 6031 | 07/20/00 | FRAP | Y | N | Undecided- may do surgery sometime during the winter | - | - |

# ANNUAL REPORT – YEAR TWO

## LABORATORY CORE

**Core Director** **Andrew K. Godwin, Ph.D.** **Fox Chase Cancer Center**

**INTRODUCTION:**

The molecular genetic events involved in the development of ovarian cancer are poorly understood. Ovarian cancer is the number one gynecologic killer in the United States with over 25,000 diagnosed cases and 14,500 deaths in 1999. A major reason for the high morbidity and mortality associated with ovarian cancer relates to the patterns of dissemination and the absence of signs or symptoms associated with early stage disease. Consequently, most patients are diagnosed with advanced stage (International Federation of Gynecology and Obstetrics [FIGO] III-IV) disease; five-year survival rates for this group of patients are only 20-30%. In contrast, five-year survival rates for patients with limited-stage disease (FIGO I-II) are 70-90%. Thus, understanding the etiology of ovarian cancer remains an important challenge in molecular genetic research. Ultimately, this knowledge may enable the development of better approaches for earlier diagnosis, allowing current therapeutic strategies to be more effective. To support these kinds of studies large numbers of biosamples from well staged and managed cancer patients and controls is needed. Therefore, the laboratory core was created to collect normal and tumor ovarian tissue as well as blood samples that can be made available for a variety of researcher projects.

**BACKGROUND:**

The Laboratory Core of the Ovarian Cancer Prevention Program of Fox Chase Cancer Center funded by the Department of Defense, is responsible for the collection, storage, and distribution of biosamples collected as a result of the "Ovarian Cancer Consortium for Research and Surveillance (OCCRS)" and the "Evaluation of Fenretinide as a Chemopreventive Agent for Ovarian Cancer".

**BODY:**

**Statement of Work Year 2:**

Months 13-24 7) Continue the collection, processing and cryopreservation of peripheral blood lymphocytes from ovarian cancer patients and their first- and second-degree relatives. 8) Submit remaining DNAs from patients enrolled in the 4-HPR chemoprevention trial to the Genetic Susceptibility Testing laboratory for *BRCA1* and *BRCA2* evaluation. Reports of these studies will be used for genetic evaluation of preneoplastic lesions. 9) Distribute additional slides containing sections of ovaries removed for prophylaxis from women on the 4-HPR trial for histology, immunohistochemistry, and genetic analyses. 10) Distribute additional DNA isolated from paraffin embedded sporadic ovarian tumors and the patient's first-degree relatives (i.e., mother and/or father) for genetic studies. 11) Collect and process additional ovaries removed for prophylaxis from patients enrolled in the 4-HPR chemoprevention trial.

The goals of year two have been met, however the number of participants recruited into the Ovarian Cancer Consortium for Research and Surveillance (OCCRS) and the fenretinide chemoprevention study were less than predicted. Nevertheless, the number of blood samples obtained from OCCRS participants have increased steadily over the last year.

**SPECIFIC AIMS (PREVIOUSLY PROPOSED):**

***Specific Aim 1:*** ***Collection and banking of blood samples from women with ovarian cancer, and their first- and second-degree relatives as part of the*** **"Ovarian Cancer Consortium for Research and Prevention".**

Results:
Two hundred-ninty three (293) participants, including 97 ovarian cancer patients and representing 165 families are enrolled. One hundred forty-nine (149) families had one case of ovarian cancer, 25 had two cases and 10 had more than two. Ninety (90) families had both breast and ovarian cancer, supporting the clustering of these cancers in women with *BRCA1* and *BRCA2* mutations. The median age of OCCRS participants is 47 years, with a range of 16 to 89 years. The geographic base of recruitment has increased significantly due to networking with national advocacy organizations such that women in 32 states and Canada are enrolled. In support of the OCCRS (**Project 1; Ovarian Cancer Consortium for Research and Surveillance**"), the Core laboratory has collected, processed and banked biospecimens (e.g., serum, platelets, DNA, and lymphocytes) from 235 blood samples.

1) 235 blood samples have been collected through the Ovarian Cancer Consortium for Research and Surveillance.

2) 235 blood samples have been process and the serum, platelets, and lymphocytes were banked and genomic DNA isolated from "buffy coats".

3) 395 samples (either DNA or whole blood) recruited through the Ovarian Cancer Clinical Network were distributed to program project participants and FCCC Investigators (175 whole blood samples to Dr. R. Raftogianis, FCCC, 100 DNA's to A. Yeung, FCCC, and 120 DNA's to T. Hamilton, FCCC).

Change in personnel/facilities:
To improve and standardize the collection and processing of blood samples, FCCC established under the direction of Dr. Godwin, the Biosample Repository in November of 1999. This new laboratory is located on the second floor of the Cancer Prevention Pavilion and occupies ~900 square feet of space with the appropriate equipment including liquid nitrogen freezer space to bank ~72,000 cryovials.

Ms. J. Dangel, Chief Technician in the Department of Pathology at the Fox Chase Cancer Center, was appointed manager of the Biosample Repository and was responsible for getting it CAP accredited and CLIA approved. Her roll is to process blood samples submitted to the Repository (through the Ovarian Cancer Consortium for Research and Surveillance. Samples to be tested for mutations in *BRCA1* and/or *BRCA2* are submitted to Clinical Molecular Genetic Laboratory. Ms. Dangel is also responsible for entering collection data regarding the biospecimens into the centralized computer database.

***Specific Aim 2:*** ***Collection and distribution of archival ovarian tumor and prophylactic oophorectomy specimens as part of the*** **"Ovarian Cancer Consortium for Research and Prevention".**

Results:
1) 28 ovarian tumor specimens were collected following surgery at Fox Chase/American Oncologic Hospital and were flash-frozen and stored in liquid nitrogen.

2) 96 ovarian fresh-frozen ovarian tumors were given to Dr. J. Testa (FCCC) to evaluate the levels of activity of AKT, AKT2, and AKT3.

3) 22 DNA's from ovarian tumor showing LOH on 6q (and matching constitutive DNA-see above) were given to Dr. T. Hamilton to support mutational analysis of *LOT-1*.

4) In the past year we have collected ovarian tissue from 37 women, ages ranging from 36 to 79 years of age. The samples have been collected from 27 different hospitals throughout the United States. Tissue collected at sites other than Fox Chase are arranged through the attending pathologist at the off campus site and a kit is mailed to either the surgeon or the pathologist.

a) Eight (8) of the women were determined to have a *BRCA1* mutation.

b) Three (3) of the women were determined to have a *BRCA2* mutation.

c) Three (3) of the women are from families with a mutation in *BRCA1* (2) or *BRCA2* (1). However, the individuals have declined clinical genetic testing. We are currently screening DNA samples isolated from ovarian tissues to determine if the women from these *BRCA1* or *BRCA2* mutation families are carriers.

d) Thirteen (13) are from families with a history of breast/ovarian cancer which have not yet been tested for *BRCA1* or *BRCA2* mutations

e) Eleven (11) are from families with no family history of breast or ovarian cancer, which have tested negative for a *BRCA1* or a *BRCA2* mutation.

f) Tissue sections of all of the ovaries were given to Dr. A. Klein-Szanto for immunohistochemical staining of various markers and pathological review.

5) Primary cell lines were generated from the ovaries of the *BRCA1* and *BRCA2* mutation carriers as well as control individuals.

a) These cell cultures are being used in a collaborative study with Dr. A. Knudson (Senior Member, FCCC) entitled "Evaluation of *in vivo* and *in vitro* pharmacology and toxicology of preventative agents using human mutant cells from dominantly heritable cancers" to study the changes in gene expression following treatment with a variety of chemoprevention agents in culture.

6) Three primary human ovarian surface epithelial (HOSE) cell cultures and 3 mortal, SV40 expression and 3 matching immortal SV40 expressing HOSE cell lines were given to Drs. P. Engstrom (P.I.) and C. Patriotis (Associate Member, FCCC) for evaluation of changes in gene expression patterns following 4-HPR treatment.

***Specific Aim 3: Collection and processing of prophylactic oophorectomies from women participating in the chemoprevention trial as part of the* "Evaluation of Fenretinide as a Chemopreventive Agent for Ovarian Cancer".**

Results:

In order to find women eligible for the 4-HPR trial, we have tested a number of participants of the FRAP for mutations in *BRCA1* and/or *BRCA2* as outlined below. Genetic testing is not funded through this application, but is necessary to increase the pool of women likely to elect to undergo prophylactic surgery.

1) DNA samples from a total of 493 individuals were tested (either partially or completely) for mutations in *BRCA1* and/or *BRCA2* during the last year

a) 493 DNA samples were tested for three Ashkenazi Jewish founder mutations (i.e., 185delAG and 5382insC for *BRCA1*, and 6174delT for *BRCA2*) using a Heteroduplex Mobility Assay (HMA).

b) 45 samples were tested for mutation in 23 exons and a limited number of adjacent intronic base pairs of *BRCA1* using an enzymatic mutation detection (EMD) assay and direct sequencing.

c) 59 samples were tested for mutations in 26 exons and a limited number of adjacent intronic base pairs of *BRCA2* using the EMD assay and/or direct sequencing.

i) 14 by direct sequencing

ii) 45 by EMD and direct sequencing

2) Genetic test results were given to Dr. M. Daly (Member, Director of the Family Risk Assessment Program) and *BRCA1* and *BRCA2* mutation carriers were approached for participation in the 4-HPR chemoprevention trial.

3) Ovarian tissue specimens were collected from 2 women who elected to undergo prophylactic oophorectomies at Fox Chase

a) The two women that participated on the 4-HPR trial reported a family positive family history of breast and ovarian cancer, but had not been previously tested for a *BRCA1* or a *BRCA2* mutation.

b) Tissue sections of all of the ovaries were given to Dr. A. Klein-Szanto for immunohistochemical staining of various markers and pathological review.

c) DNA was isolated from the ovarian tissue and is being evaluated in the Clinical Molecular Genetics Laboratory for mutations in either *BRCA1* or *BRCA2*.

4) A limited number of DOD participants have been tested for germline mutations in *BRCA1* and/or *BRCA2*. Six (6) *BRCA1* and one (1) *BRCA2* mutations have been detected in just 16 of the participants which were randomly selected and six (6) mutations (five in *BRCA1* and one in *BRCA2*) were uncovered in 24 women of Ashkenazi Jewish heritage. Further studies by our group are scheduled to determine the prevalences of germline *BRCA1* and *BRCA2* mutations in population-based samples of ovarian cancer cases in the U.S. and Canada (as indicated below).

**KEY RESEARCH ACCOMPLISHMENTS:**

-Obtained 200 blood samples into the OCCRS in the past 12 months.
-Distributed DNA from blood and ovarian tumors to multiple investigators for various studies (as outlined below).
-Collected 37 overtly normal ovaries from women undergoing oophorectomies. Two of these individuals had participated on the 4-HPR chemoprevention trial.
-Identified 13 germline mutations in the OCCRS participants.

**REPORTABLE OUTCOMES**:

-In total we have collected 64 ovaries (27 women donated both their left and right ovaries, 6 donated only the left ovary, and 4 donated only the right ovary). We have successfully initiated HOSE cell cultures from 50 of these tissues.

**CONCLUSIONS:**

Collection of ovarian cancer tissue (tumor and normal) and blood biospecimens is ongoing, due in part to the high compliance rate of the participants. Laboratory research is underway using DNA from these samples to:

1) Determine the prevalence of germline *BRCA1* and *BRCA2* mutations in population-based samples of ovarian cancer cases in the U.S. and Canada
2) Estimate the penetrance of germline *BRCA1* and *BRCA2* mutations and compare these estimates across:
    a) genes (BRCA1 vs. BRCA2)
    b) mutation type (Ashkenazi Jewish founder mutations vs. all others)
    c) method of family ascertainment
3) Identify novel genetic polymorphisms in the human arylsulfatase gene from 100 samples; a SNP in the 3'-flanking region has been identified.
4) Identify common alleles in the human UDP-glucuronosyltransferase gene, UGT1A6. Thus far four common alleles have been identifies and will be further characterized for functional significance with funding from a DOD Breast Award.
5) Identify novel genetic polymorphisms in the human sulfotransferase gene, SULT2B1; this project is in the beginning stages.
6) Determine if *LOT*-1 on chromosome 6q is maternally imprinted and if loss of the paternal allele is involved in ovarian carcinogenesis.

Overall, the studies outlined above that are utilizing the valuable resources collected through the Core laboratory will provide important insights with regard to molecular genetic mechanisms associated with ovarian epithelial oncogenesis as well as a better understanding of the biological and biochemical pathways which are altered in response to chemopreventive treatments.

# ANNUAL REPORT – YEAR TWO

## DATA MANAGEMENT CORE

**Core Director** **Eric A. Ross, Ph.D.** **Fox Chase Cancer Center**

**Introduction:**

The varied populations studied in this Ovarian Cancer Prevention Program and the complexity of the designs requires the development and support of program-specific computer based tools to provide critical project management and coordination, and for the collection, validation, storage, retrieval and analysis of data. The projects contained in this program project grant (PPG) include: the Ovarian Cancer Consortium for Research and Surveillance, the Facilitating Decision-Making About Prophylactic Oophorectomy, and the Phase II Chemoprevention Study of Ovarian Cancer studies.

The specific aims of the Data Management Core (Core) are:

1. Provide computer-based tools that facilitate the entry, storage, manipulation and retrieval of the large quantities of data generated.
2. Ensure the accuracy of the data maintained in the database by developing human and software based data consistency and quality control systems.
3. Provide high-quality data entry services.
4. Organize and maintain the database to maximize accessibility, while maintaining strict confidentiality.
5. Provide statistical computing support.

**Body:**

**Statement of Work Year 2:**

*Months 3-36:* (1) Data quality assurance and quality control procedures will be developed and implemented. (2) Research staff will be instructed in data coding procedures. (3) The Data Entry Clerk and laboratory technicians will be trained in the use of the electronic data entry forms. All data delivered to the Core will be efficiently and accurately entered by the Data Entry Clerk into the database. (4) Post-data entry, data validation software will be developed, tested and utilized. All data will be reviewed upon receipt and aberrant values will be corrected. (5) Daily backups of the database will be conducted.

*Months 6-36:* (1) The Database Programmer will perform all tasks necessary to ensure that the database functions in an efficient manner. The database will be modified by the Database Programmer, as necessary, to ensure that the database software meets the needs of the projects that compose the Program Project. (2) Software for the generation of reports concerning each study's progress will be developed, tested and periodically executed. (3) Software to allow for the extraction of data for analysis purposes will be developed, tested and utilized upon request. (4) Statistical programming tasks may be conducted by Core staff under the direction of the study statisticians.

The goals of year two have been met. These tasks will continue through year three.

**Key Research Accomplishments**

- This core has designed and developed a comprehensive information management system to meet the specific needs of this PPG. The customized relational database system has been implemented using ORACLE version 8 database software. The database and management structure allows efficient data capture and manipulation, as well as the controlled exchange of information across the several projects.
- Client-server electronic data entry/retrieval and report generation software have been developed using the Oracle Developer/2000 suite of products. Example electronic data entry screens can be found in Appendix 1.
- Data entry services are being provided by a Core data entry clerk using the electronic data entry screens developed by Core programmers.
- Data quality assurance procedures have been implemented, using software-based data entry checks as well as post-entry manual audits.
- Software has been developed to generate reports to allow tracking of study accrual and progress of individual study subjects.
- Software has been developed for extracting data from the relational database.
- Core personnel support all aspects of the information management system.
- The database is backed-up to tape on a daily basis. Periodically, a copy of the database backup tape is sent to an off-campus facility for secure storage.

**Reportable Outcomes:**

All data collected in the three research projects as well as data generated by the Laboratory Core are being stored in this information system. The details of the information system developed for this the three research projects are described below.

*Project I: The Ovarian Cancer Consortium for Research and Surveillance:*

Included in this portion of the PPG information system is health history, clinical, epidemiologic, socio-demographic, psychosocial and laboratory data. In addition, this database contains cancer and vital status data on relatives of individuals recruited into the study. The software system coordinates numerous tasks, including the scheduling of follow-up visits, the distribution of mailed self-report questionnaires, and the generation of contact logs for conducting telephone interviews. This system is capable of generating multigenerational pedigrees from the union of family histories provided by two or more distinct study subjects in the same family. The family data is easily updated from follow-up information to include deaths or new cancers reported for study subjects, previously listed family members, as well as new births. Currently, data from 293 participants are stored in this database.

*Project II: Facilitating Decision-Making About Prophylactic Oophorectomy:*

The database system provides the means for entry, storage and manipulation of all the psychosocial, outcome and study-related data collected in this project. Software has been

developed to automatically distribute mailed self-report questionnaires. Information obtained from 76 study subjects have been entered into the information system.

*Project III: Phase II Chemoprevention Study of Ovarian Cancer:*

The PPG relational database management system also maintains all of the information collected in this phase II clinical study including demographic, health history, pathology, laboratory, study status, adverse reaction and drug compliance data. The software system facilitates many aspects of data collection and patient tracking. This software system uses database information to perform such tasks as: determination of study eligibility, automated subject randomization, and automatic notification of the study biostatistician (via e-mail) of subject randomization. Since initiating the study, three subjects have been identified as eligible for the protocol. One subject has been randomized.

**Conclusions:**

Ovarian cancer is the leading cause of death from a gynecologic malignancy among women in the United States, and ranks second in incidence among gynecologic malignancies. The Fox Chase Cancer Center is conducting research in ovarian cancer prevention and control focusing on familial risk of cancer, the behavioral factors influencing the decision to undergo prophylactic oophorectomy, and the effect of chemoprevention agents on precancer structural and molecular markers of carcinogenesis.

This core is intended to be a resource for the PPG as a whole, and to maintain a valuable source of data for future studies. By centralizing these services into a Data Management Core, we are better able to manage and coordinate the collection, storage, and distribution of a large amount of highly valuable data. Subject to informed consent, the information contained in the data repository is available to all investigators in the PPG. By providing access to the data to all participants, sharing technical capabilities and ensuring the quality of the data, this core will not only facilitate achievement of the aims of the individual projects, but also encourage exploratory analyses beyond the stated aims of the projects.

FOX CHASE
CANCER CENTER

*7701 Burholme Avenue*
*Philadelphia, Pennsylvania 19111*

October 26, 2000

The IRB Committee assures that all key personnel on this grant application will acquire certification as follows:

FCCC - Requirements for education and training in protection of human subjects involved in research:

1) All investigators, applicable staff, and administrators must complete an approved education and training program on human subjects research and be certified annually. The FCCC Institutional Review Board (IRB), in collaboration with the National Comprehensive Cancer Network (NCCN) and the University of Miami has established a web-based modular training program. To be certified the investigator must complete all 13 parts of the training module and answer the quizzes at the end of each module. The modular online course includes the following units: History, Ethical Principles, Regulation and Process, Informed Consent, Research with Investigational Drugs and Devices, Behavioral Research, Prisoners, Minors, Pregnant Women and Fetuses in Utero, Decisionally Impaired Subjects Economically & Educationally Disadvantages subjects, Record-based Research, Genetic Research, and Research Integrity. The University of Miami provides the certification of successful completion of the program.

2) All investigators must complete an Investigator Attestation Form, indicating that they will abide by all FDA and other federal regulatory requirements for the conduct of human research involving humans.

3) All investigators, staff and administrators must complete a Conflict of Interest Statement annually and update it as necessary.

The FCCC IRB considers research on human blood and tissues, even if obtained from a repository, to be human subjects research. Therefore, investigators involved in such activities must comply with the requirements listed above.

Michael H. Levy, M.D., Ph.D.
Acting Chairman, Institutional Review Board

## APPENDICES

A. **Project I, Key Personnel**

B. **Project I, Development of an Ovarian Cancer Symptom Checklist Consent Forms**

C. **Project I, Focus on Ovarian Cancer Research Information Flyer**

D. **Project II, Publication: Decision Making about Prophylactic Oophorectomy among At-Risk Women: Psychological Influences and Implications**

E. **Data Management Core, Example Electronic Data Entry Screens**

# APPENDIX A

# PROJECT I

# KEY PERSONNEL

## Fox Chase Cancer Center

Principal Investigator: Paul F. Engstrom, M.D.
Project Director: Mary B. Daly, M.D., Ph.D.
Co-Investigator: Andrew Godwin, Ph.D.
Co-Investigator: Betsy Bove, Ph.D.
Statistician: Andre Rogatko, Ph.D.
Project Manager: Carol Cherry, R.N.C., B.S.N., O.C.N.
Genetic Counselor: Josephine Costalas, M.S.
Administrative Assistant: Honey Salador
Data Management: Andrew Balshem
John Malick
Rose Batson
Director of Nursing Research: Andrea Barsevick, R.N., D.N.Sc.

## Cooper Hospital/University Medical Center

Network Site Director: Generosa Grana, M.D.
Gynecology Oncology Group: David Warshal, M.D.
James Aikins, M.D.
Thomas Rocereto, M.D.
Genetic Research Coordinator: Evelyn Churchville Letarte, A.D.
Gynecologic Oncology Nurse: Wendy Topeka, R.N., B.S.N., O.C.N.

## The Reading Hospital and Medical Center

Network Site Directors: Norman G. Rosenblum, M.D., Ph.D. & Terrance Cescon, M.D.
Cancer Center Program Manager: Patricia Weiser, R.N., C.C.R.A.
Family Risk Assessment Program Coordinator: Marilyn Brennan, R.N., O.C.N.

## Wake Forest University Baptist Medical Center

Network Site Director: Electra D. Paskett, Ph.D.
Research Fellows: Lauren Bliss, M.D.
Kristie Long, Ph.D.

# APPENDIX B

## PROJECT 1

**Development of an Ovarian Cancer Symptom Checklist**
**Consent Forms (Approved April 12, 2000)**

IRB #98-820

**Informed Consent to Participate in Research Studies**



**Title of Study:** Development of an Ovarian Cancer Symptom Checklist (Focus Group)

**Principal Investigators:** Mary B. Daly, MD, PhD
Carol Cherry, RNC, BSN, OCN
Family Risk Assessment Program
Fox Chase Cancer Center
7701 Burholme Avenue
Philadelphia, PA 19111
Telephone: (215) 728-3672 or (800) 325-4145

**Purpose:** The Family Risk Assessment Program of Fox Chase Cancer Center recognizes the need for better ways to diagnose ovarian cancer at as early a stage as possible, so that patients may have an improved quality of life. I have been asked to participate in a research study to identify symptoms that may indicate early ovarian cancer. This information will help the researchers identify common symptoms and develop a checklist. It is hoped that this tool will be useful in educating both women and medical professionals, and lead to earlier diagnosis.

**Study Participants:** I have been asked to participate in this study because I am a woman who has been diagnosed with ovarian cancer.

**Procedures:** I am voluntarily participating in a focus group where I'll be asked to describe the physical changes I experienced prior to my diagnosis of ovarian cancer, as well as the process of having medical evaluation. I will be completing a short registration form upon arrival to a session that will last up to two hours. I understand that the session will be audiotaped.

**Potential Risks:** It is possible that describing my experiences may cause an emotional response within myself. I understand the staff will be sensitive to my feelings.

**Benefits:** Although there are no direct benefits to myself for participating in this study, it is hoped that the outcome will benefit others in the future.

**Confidentiality:** All personal information obtained for this study will be kept confidential. I understand that information obtained on audiotape or by written questionnaires will be kept in a secure place at Fox Chase Cancer Center. This information will be added to computer data files. The results may be published or presented to scientific groups, but I will not be identified by name in these publications.

**Voluntary Consent:** For additional questions concerning this study or if I am not satisfied with the manner in which it is being conducted, I may contact the principal researcher, Dr. Mary Daly, at (215) 728-2791 or the study project manager, Carol Cherry, at (215) 728-3672. Or I may report (without giving my name if I so choose) any complaints to the Institutional Review Board by calling (215) 728-2518, 9:00a.m. to 5:00p.m. Monday through Friday, or by addressing a letter to the Institutional Review Board at Fox Chase Cancer Center, 7701 Burholme Ave., Philadelphia, Pa 19111. By signing below, I indicate that I have read this form, received acceptable answers to my questions, and have agreed to participate in the study, as described above. I will receive and keep a copy of this form.

| | | |
|---|---|---|
| Signature of Participant | Printed Name | Date |
| Signature of Witness | Printed Name | Date |

**March 3, 2000**

IRB #98-820

**Informed Consent to Participate in Research Studies**



**Title of Study:** Development of an Ovarian Cancer Symptom Checklist (Questionnaire Evaluation)

**Principal Investigators:** Mary B. Daly, MD, PhD
Carol Cherry, RNC, BSN, OCN
Family Risk Assessment Program
Fox Chase Cancer Center
7701 Burholme Avenue
Philadelphia, PA 19111
Telephone: (215) 728-3672 or (800) 325-4145

**Purpose:** The Family Risk Assessment Program of Fox Chase Cancer Center recognizes the need for better ways to diagnose ovarian cancer at as early a stage as possible, so that patients may have an improved quality of life. I have been asked to participate in a research study to identify symptoms that may indicate early ovarian cancer. This information will help the researchers identify common symptoms and develop a checklist. It is hoped that this tool will be useful in educating both women and medical professionals, and lead to earlier diagnosis.

**Study Participants:** I have been asked to participate in this study because I am one of the following: 1) a woman diagnosed with ovarian cancer, or 2) a woman with a family member diagnosed with ovarian cancer, or 3) a healthy woman.

**Procedures:** I am voluntarily participating in this study where I'll be asked to complete a questionnaire about symptoms of ovarian cancer. My answers will help the researchers determine if the questionnaire is easy to read and understand, and provides a scientifically sound method for measuring symptoms.

**Potential Risks:** It is possible that describing my experiences may cause an emotional response within myself. I understand the staff will be sensitive to my feelings.

**Benefits:** Although there are no direct benefits to myself for participating in this study, it is hoped that the outcome will benefit others in the future.

**Confidentiality:** All personal information obtained for this study will be kept confidential. I understand that information obtained by written questionnaires will be kept in a secure place at Fox Chase Cancer Center. This information will be added to computer data files. The results may be published or presented to scientific groups, but I will not be identified by name in these publications.

**Voluntary Consent:** For additional questions concerning this study or if I am not satisfied with the manner in which it is being conducted, I may contact the principal researcher, Dr. Mary Daly, at (215) 728-2791 or the study project manager, Carol Cherry, at (215) 728-3672. Or I may report (without giving my name if I so choose) any complaints to the Institutional Review Board by calling (215) 728-2518, 9:00a.m. to 5:00p.m. Monday through Friday, or by addressing a letter to the Institutional Review Board at Fox Chase Cancer Center, 7701 Burholme Ave., Philadelphia, Pa 19111. By signing below, I indicate that I have read this form, received acceptable answers to my questions, and have agreed to participate in the study, as described above. I will receive and keep a copy of this form.

| | | |
|---|---|---|
| Signature of Participant | Printed Name | Date |
| Signature of Witness | Printed Name | Date |

**March 3, 2000**

# APPENDIX C

## PROJECT 1

**Focus on Ovarian Cancer Research Information Flyer**

Family Risk Assessment Program

# FOCUS ON OVARIAN CANCER RESEARCH

## Ovarian Registry Growing Strong

The Ovarian Cancer Consortium for Research & Surveillance, referred to as the OCCRS or Ovarian Registry, is into its second year and growing steadily. This research effort funded by the Department of Defense is collecting family and lifestyle information, blood and tumor tissue from families with a history of ovarian cancer. Samples are stored at Fox Chase Cancer Center (FCCC) to serve as a resource for future studies in prevention, detection and treatment of this disease. The work of the Ovarian Registry is expanding due to collaboration with Reading Medical Center in Reading, PA, Cooper Medical Center in Camden, NJ, and Bowman Gray Medical School, affiliated with Wake Forest University in Winston-Salem, NC. Our staff have been inspired by the interest of ovarian cancer patients and families to participate (see story right). Recruitment has been enhanced through networking with advocacy organizations and, to date, 296 patients and family members representing 29 states and Canada have been recruited (see map). The dedication of families affected by ovarian cancer is greatly appreciated. For more information please call ***Honey Salador or Carol Cherry at (215) 728-3504 or (800) 325-4145.***

## Registry Participants Inspire Staff

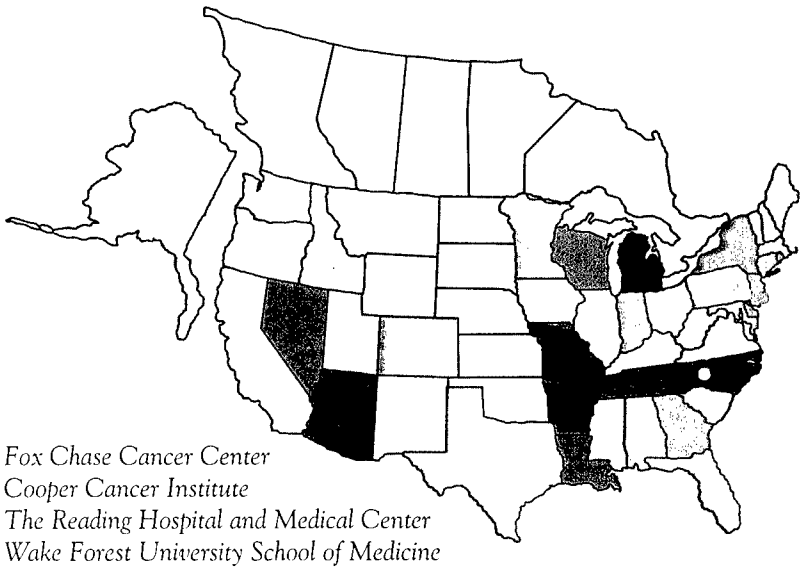
I would like to take this opportunity to sincerely thank all of the participants and families of the OCCRS for your dedication to this research effort. Recruitment for the Ovarian Registry is strong and smooth, due in a large part to everyone joining together to help reach our goals. You have been an inspiration to all of us here at Fox Chase Cancer Center through your dedication to this cause.

I would especially like to mention one of our participants, Cheryl Ann Gremaud Duvall, who lost her battle with ovarian cancer on March 8, 2000. My contact with Cheryl was limited to phone recruitment and follow-up calls for the Ovarian Registry, but in that short period of time I came to know what a very special person she was. Cheryl was in the end stages of her disease when I first spoke to her, but she was determined to donate a blood sample. She contributed the sample a few days prior to her death. I was informed of Cheryl's passing by her parents, Ronald and Judy Gremaud, when I phoned them to see if they were interested in participating in the Ovarian Registry. After speaking with Judy, I learned of Cheryl's courageous 27-month battle. I am honored and grateful to have had the opportunity to help her realize her goal to participate in the Ovarian Registry.

Honey

*Honey Salador*
*Recruitment Specialist*

*Locations Representing OCCRS Participants in the US and Canada*



- *Fox Chase Cancer Center*
- *Cooper Cancer Institute*
- *The Reading Hospital and Medical Center*
- *Wake Forest University School of Medicine*

# A FULL CIRCLE OF OVARIAN CANCER PREVENTION RESEARCH

Fox Chase Cancer Center (FCCC) is one of a growing number of research institutions to receive funding from the Department of Defense (DOD) for ovarian cancer studies. Beginning in fiscal year 1997, ovarian cancer was added to the list of medical research priorities supported by the DOD. This funding is due in part to the persistent efforts of cancer advocacy organizations that tirelessly work for increased awareness of the disease. A summary of the DOD funded ovarian cancer prevention research at FCCC is outlined below.

## Ovarian Cancer Consortium for Research & Surveillance (OCCRS)

*This family registry creates a large database to support current and future research.*

### *Ovarian Cancer Symptom Checklist Project*

The goal of this OCCRS companion project is to characterize the symptoms prior to ovarian cancer diagnosis. The results of interviews with newly diagnosed patients will be used to design a symptom checklist survey. The survey will be tested to design a valid tool for health care professionals to better recognize and evaluate ovarian cancer symptoms at an earlier stage.
***Contact Carol Cherry @ 1-800-325-4145***

### *Facilitating Decision Making About Prophylactic Oophorectomy*

The psychological impact of ovarian cancer risk and how it prompts women to decide for or against the removal of healthy ovaries is the focus of this study. Women, age ≥18 who have had *BRCA1/2* genetic testing or who have had a mother, sister, daughter, aunt or grandmother diagnosed with ovarian cancer are asked to complete questionnaires at four time-points.
***Contact Maggie Longacre @ 215-728-7042***

### *A Phase II Evaluation of Fenretinide as a Chemopreventive Agent for Ovarian Carcinoma*

Women, age ≥18 who have decided after genetic risk assessment to undergo removal of their ovaries to help prevent ovarian cancer, will take either a placebo or Fenretinide (a Vitamin A derivative) for four to six months prior to surgery. When the ovaries are removed, they will be studied to learn how effective the drug is in stopping precancerous changes.
***Contact Cecilia McAleer @ 215-728-2981 or call 1-800-ENROLL ME (1-800-367-6556)***

### *Quality of Life after Prophylactic Oophorectomy*

In direct response to requests of cancer survivors, this study was designed to document how preventive removal of ovaries impacts on lifestyle issues such as menopausal symptoms, sexual functioning, anxiety and self-concept. Women who have considered and then decided for or against prophylactic oophorectomy will be asked to complete questionnaires at four time-points.
***Call Carol Cherry @ 1-800-325-4145***

## *Hot off the Press...*

***Resources, A Guide for Women Living with Ovarian Cancer,*** is a complete resource guide full of useful, supportive information for a woman's journey with ovarian cancer. This book is available free of charge through Bristol-Myers Squibb Oncology. Ask your doctor to request publication K4-FO24 from a contact with that company.

FOX CHASE
CANCER CENTER

# APPENDIX D

## PROJECT II

**Publication: Decision Making about Prophylactic Oophorectomy Among At-Risk Women: Psychological Influences and Implications**

Gynecologic Oncology 75, 406–412 (1999)
Article ID gyno.1999.5611, available online at http://www.idealibrary.com on IDEAL®

# Decision Making about Prophylactic Oophorectomy among At-Risk Women: Psychological Influences and Implications[1]

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Received May 17, 1999

*Objective.* Women with a family history of ovarian cancer are confronted with difficult decisions regarding the management of their risk status. Currently, the main preventive option available is prophylactic oophorectomy. The objective of the present paper is to review research and theory on psychological factors that influence decision making about preventive surgery and discuss the implications for patient management.

*Methods.* Guided by a cognitive–social framework, the literature on decision making about preventive surgery is reviewed and integrated.

*Results.* The available studies show that women are more likely to opt for surgery if they feel more vulnerable to cancer, believe that surgery will prevent cancer, and are worried about developing cancer. Further, the response to ovarian risk is influenced by the individual's characteristic psychological style: monitors (who typically scan for and amplify threatening cues) tend to feel more vulnerable to cancer and more distressed about their cancer risk than blunters (who typically distract from threatening cues) do.

*Conclusion.* On the basis of prior research, monitors may be more likely to choose surgical intervention to reduce their distress, without fully anticipating the psychological and medical consequences of that decision. In order to facilitate informed decision making, counseling protocols should be designed to enable the patient to understand and take account of the psychological consequences of the available medical options. Future studies are needed to systematically extend and explore the proposed theory-based relationships. 

*Key Words:* ovarian cancer risk; prophylactic oophorectomy; monitoring vs blunting.

## OVERVIEW

Ovarian cancer is associated with the highest mortality rate among all of the gynecological cancers [1], resulting in more than 14,500 deaths each year in the United States [2]. The high incidence of ovarian-cancer-related mortality is believed to be due to two main factors. First, no distinctive symptoms have been identified in patients at the early stages of disease [2, 3]. Second, currently available surveillance methods have not proven to be highly reliable in detecting early stage disease [2, 3]. The challenges posed by the limitations of early detection are of particular concern in the case of patients at increased familial risk for ovarian cancer [4]. One medical strategy being offered to these women is prophylactic oophorectomy, that is, the surgical removal of healthy ovaries [4, 5]. The information that needs to be conveyed about this preventive option is complex, making it difficult for patients to accurately weigh the costs and benefits of alternative choices.

To date, few empirical data are available on how at-risk women understand and make decisions about prophylactic surgery. As a result, little is known about how to communicate necessary information in a manner that optimizes decision making and enhances patient adaptation to the decisions made. In the present paper, we briefly review the medical issues facing women at familial risk for ovarian cancer, particularly with respect to their preventive options. We describe a cognitive–social theoretical framework that delineates the psychological factors that play a role in the decision-making process. We then illustrate two prototypic styles of processing ovarian cancer risk feedback, monitoring vs blunting, and describe how they influence and interact with the psychological factors that influence decision-making processes. Finally, we discuss the implications of the current findings for counseling protocols designed to enhance decision making about prophylactic oophorectomy.

## PREVENTIVE OPTIONS FOR OVARIAN CANCER RISK

Epidemiological evidence has identified family history as one of the major risk factors for ovarian cancer [2, 6]. First-degree relatives (FDRs: i.e., mother, sister, or daughter) with one affected family member have a lifetime risk of 5%, which is more than three times the 1.4% lifetime risk for women without a family history [2, 7]. For women with two affected family members, the lifetime risk rises to 7% [2]. Further, women who have a genetic susceptibility to breast and/or ovarian cancer (i.e., who are carriers of a *BRCA1/2* genetic

[1] This study was supported by National Cancer Institute Grants CA58999, CA61280, CA06927, CA57379, CA65727, and CA76644, Human Genome Research Institute Grants HG01766 and HG01189, and Department of Defense Grants BC971638 and OC970004.

0090-8258/99 $30.00

mutation) have a 16 to 65% lifetime risk of developing ovarian cancer [8].

Patients presenting with localized disease have a 79% 5-year survival rate. Yet, despite significant interest in improving early detection of ovarian cancer [6], 75% of all ovarian cases present with advanced stage disease [9]. Advanced stage disease is difficult to treat effectively and is associated with an alarmingly low 5-year survival rate of approximately 28% [10]. Contributing to this high mortality rate are two factors: (1) the absence of well-recognized signs and symptoms during the early stages of disease, and (2) the fact that the available surveillance methods have relatively poor sensitivity and specificity [2].

Since effective detection and management strategies for ovarian cancer are limited, preventive options become important, particularly for women at increased risk for disease. Current methods include the use of oral contraceptives and tubal ligation [2, 6, 11–14]. For example, oral contraceptive use for 6 or more years is associated with a 60% reduction in risk among women who carry *BRCA1* or *BRCA2* mutations [15]. However, the studies conducted to date have not resolved the issue of whether the potential benefits (i.e., ovarian cancer risk reduction) outweigh the possible risks (i.e., increased breast cancer risk; [16–19]) for high-risk women. Hence, these approaches have not been routinely incorporated into standard care.

A primary surgical preventive option available for high-risk women is prophylactic oophorectomy, that is, the surgical removal of noncancerous ovaries [2, 4, 20, 21]. Studies have shown that prophylactic oophorectomy significantly reduces ovarian cancer risk in pre-, as well as post-, menopausal women [22, 23]. It has been estimated that a 30-year-old woman with hereditary breast–ovarian cancer syndrome can gain from 0.3 to 2.6 additional years of life expectancy as a result of prophylactic oophorectomy [24, 25]. A recent study using a Markov model showed that high-risk women (i.e., those with an affected relative and a positive *BRCA1/2* mutation status) would live longer if they undergo prophylactic surgery [25]. On the other hand, the benefits of prophylactic surgery appear to be small or nonexistent for women at lower risk [25]. Gains in life expectancy decline with age at the time of surgery and appear to be minimal for women 60 years of age and older [24].

Along with the potential medical benefits, patients inclined to undergo prophylactic oophorectomy must also consider the potential limitations of the procedure [2, 6, 20, 26]. First, the surgery does not appear to completely eliminate cancer risk. Although the data are limited, cases of postoophorectomy intra-abdominal carcinomatosis (which histologically resembles ovarian cancer) have been reported in the literature [23, 26, 27]. Like ovarian cancer, peritoneal cancers are also difficult to detect at an early stage, and thus, women contemplating prophylactic oophorectomy need to consider whether they will continue to feel vulnerable to cancer, even after they have had their ovaries removed [28].

Second, the surgical procedure itself is associated with certain risks (e.g., surgical morbidity and postsurgical complications), particularly for those women who are not candidates for laparoscopic surgery. Further, surgery can entail a lengthy hospital stay and recuperative period and may be complicated by adhesions and small bowel obstruction. Third, estrogen deprivation following prophylactic oophorectomy results in an elevated risk for heart disease and osteoporosis [29]. To counteract these effects, patients are advised to undergo a prolonged regimen of hormone replacement therapy (HRT). HRT may be associated with increased risk for breast cancer [30–32], which may raise anxiety and interfere with compliance. Indeed, published reports suggest that between 11 and 69% of women are noncompliant with HRT [33, 34]. Fourth, for women of reproductive age, the loss of future childbearing potential may represent a source of emotional distress [28].

Women who are inclined to forego prophylactic oophorectomy need to consider two main potential limitations. First, they may have to deal with sustained perceptions of vulnerability, since available detection methods are not highly reliable [2, 6]. Second, the necessity of undergoing repeated ovarian screening (e.g., a bimanual rectovaginal examination, transvaginal ultrasonography with Doppler flow, and serum blood testing for the antigenic CA-125 tumor marker) may cause distress, as the surveillance may serve as a continuous reminder of one's vulnerability to disease. Given that there is no medically "right" or "wrong" preventive recommendation for at-risk women, the decision about whether to undergo prophylactic oophorectomy needs to take an in-depth account of the psychological consequences of each option for a given individual [35].

## A COGNITIVE–SOCIAL THEORETICAL FRAMEWORK FOR DECISION MAKING ABOUT PROPHYLACTIC OOPHORECTOMY

Decades of research have shown that individuals make judgments about how to manage perceived health risks in ways that cannot be understood primarily in terms of the statistical considerations on which rational decision-making models are based [36, 37]. This is particularly likely to be the case when the information they receive is emotionally threatening and the stakes are highly personal and entail significant threats to one's sense of well-being [38–40]. In the context of genetic testing for breast and ovarian cancer risk, for example, the results show that women often focus selectively on the potential benefits (e.g., gaining reassurance) and ignore the potential limitations (e.g., continued anxiety, regret) of genetic risk feedback [40–44].

The Cognitive–Social Health Information Processing (C-SHIP) model [45–48] provides a theory-based framework for guiding the application of behavioral science to understanding how at-risk women deal with the decision-making process [49–53]. The cornerstone of this approach is that a woman's decisions are determined by how she cognitively and emotionally processes infor-

mation about her cancer risk [e.g., 49, 54–57]. In this approach, decision making is influenced by three main factors: (1) how the patient construes her vulnerability to disease (i.e., her perceived susceptibility to ovarian cancer); (2) the patient's expectancies and beliefs about the efficacy of available courses of action (i.e., the advantages and disadvantages of prophylactic oophorectomy and repeated surveillance); and (3) the patient's affects and feelings (i.e., her worries and concerns). We now review evidence for the role of these factors in decision making about prophylactic oophorectomy, citing literature where relevant studies exist and drawing from related literature in instances where direct evidence is not yet available.

### *Health-Relevant Encodings*

Health-relevant encodings refer to how an individual appraises incoming threat and disease-relevant information (e.g., cancer risk feedback) [48]. These encodings play a role in decision making about preventive surgery among high-risk women. For example, a significantly higher percentage of women who test positive for a *BRCA1* genetic mutation (which has been found to increase perceptions of vulnerability) express interest in prophylactic oophorectomy than those who test negative (76% vs 0%; [58]). In a descriptive study of relatives from *BRCA1* families, decision making about undergoing prophylactic oophorectomy was cited as one reason for undergoing genetic testing [58]. Indeed, in a study of FDRs of breast cancer patients, women who tested positive for a *BRCA1* mutation were more inclined to consider prophylactic oophorectomy than prophylactic mastectomy [59]. The focus on prophylactic oophorectomy is understandable, given the current limitations of early detection and surveillance regimens for ovarian disease [2]. In related work with FDRs of breast cancer patients, women who expressed an interest in prophylactic mastectomy perceived their risk of disease to be higher than women who were not interested in surgery [60].

### *Health-Relevant Expectancies, Beliefs, and Values*

Health-relevant expectancies refer to the individual's self-efficacy beliefs (e.g., "I am able to comply with ovarian cancer screening recommendations"), as well as to the anticipated consequences of particular courses of action (e.g., "Undergoing prophylactic oophorectomy will reduce my chances of getting ovarian cancer"). Individuals' health values refer to the personal importance that is placed on various health outcomes, such as the ability to have children. These expectancies, beliefs, and values can have profound consequences for health behaviors [61, 62].

Health behaviors are influenced by the outcome and efficacy expectancies with regard to available courses of action, as well as the perceived quality of early detection, prevention, and treatment consequences [48]. In one study, women were highly likely to consider prophylactic oophorectomy if they believed that it would reduce their ovarian cancer risk and provide the only means by which they could guarantee their survival and thereby enable them to fulfill their social obligations [28]. On the other hand, women were less inclined to consider prophylactic oophorectomy if they believed it would upset the natural balance of their body, if they questioned the efficacy of the procedure, if they believed the operation would compromise their social obligations, or if it would result in immediate cessation of fertility [28].

### *Affect*

Women's cancer-related worries and anxieties contribute to their decisions regarding cancer prevention options. Studies of women at risk for ovarian cancer have found that they experience moderate to high levels of psychological distress [63, 64], low perceptions of control, and elevated cancer risk perceptions. For example, among 154 women with a familial history undergoing surveillance for ovarian cancer, a significant proportion (31.4%) reported experiencing high levels of depressive symptoms and 16% exhibited elevated levels of anxiety [64].

The affective consequences of the individual's cancer risk status appear to have implications for her decisions regarding prophylactic surgery. Notably, women who are more worried about their breast cancer risk are also more interested in prophylactic mastectomy than are women who are less concerned [65]. Case reports also cite higher levels of anxiety in at-risk women who choose to undergo prophylactic mastectomy versus those who decline preventive surgery [66]. Thus, affective factors (e.g., worry) appear to influence women's decision-making processes in favor of preventive surgery.

### *Information Processing Styles: Monitoring versus Blunting of Ovarian Cancer Risk*

The literature reviewed above suggests that psychological factors influence women's decision making about prophylactic oophorectomy. In particular, the available findings indicate that heightened perceptions of vulnerability to ovarian cancer, as well as greater worries about ovarian cancer, are associated with greater interest in preventive surgery. Further, preliminary data indicate that women hold positive or negative expectancies regarding the outcome of the surgery, and these expectancies may be a factor in women's decision making.

Previous research has identified two main cognitive–affective processing styles that people use to deal with medical threats: monitoring versus blunting. The first processing style, monitoring, is characterized by scanning for, and amplifying, threatening cues. The second processing style, blunting, involves distraction from threatening cues [67]. Individuals with these types of information processing dynamics have been identified with the Monitoring–Blunting Style Scale (MBSS), for which extensive evidence is available [67]. In contrast to blunters, monitors tend to respond to cancer threats with higher levels of perceived vulnerability, lower levels of perceived self-efficacy and control, and heightened cancer-related distress [61, 68, 69].

In the ovarian risk context, monitors have been found to have increased perceptions of vulnerability to the disease, since they tend to scan for, and attend to, health threats pervasively [67]. In a study of first-degree relatives of ovarian cancer patients, monitors perceived themselves to be at greater risk for developing the disease than blunters, independent of their true levels of risk [69]. Increased perceptions of risk and accompanying intrusive ideation, in turn, can undermine adaptive health-protective behaviors by leading to increased levels of distress [70, 71].

Monitors and blunters also differ in their expectations of how genetic risk information will impact on them. Lerman and colleagues [68] examined interest in, and expectations about, the impact of genetic testing among 121 women who had a first-degree relative with ovarian cancer. Overall, the majority of women (75%) reported being "definitely interested" in genetic testing. However, monitors anticipated that they would react more negatively to testing feedback than blunters. That is, monitors believed that genetic testing feedback would make them more depressed and anxious in comparison with blunters [68]. Thus, although monitors expressed greater interest in knowing or learning more about their cancer risk, they also anticipated that they would respond more adversely to the psychological consequences of this information [68].

Finally, monitors and blunters have been found to differ in their affective response to ovarian cancer risk. Wardle and colleagues [72] studied at-risk women in a screening program to detect early familial ovarian cancer by ovarian ultrasound. Distress was measured before and after their first screening using the General Health Questionnaire (GHQ). Women were informed of any abnormality immediately; none of the patients were ultimately found to have ovarian cancer. Before the scan, all groups showed equivalent levels of distress. After the scan, monitors with positive (i.e., abnormal) results showed greater increases in distress compared with blunters receiving positive results and compared with patients receiving negative (i.e., normal) results. Among those undergoing follow-up scans for positive results, monitors who again tested positive showed a greater increase in anxiety than other women. Moreover, these effects were long-lived [73]. One year after having had a false-positive result, monitors reported significantly higher levels of distress and anxiety (as measured by the GHQ) than blunters. Further, monitors who underwent surgical intervention showed the highest levels of distress as measured by the GHQ [73].

## CONCLUSIONS AND FUTURE DIRECTIONS

For the foreseeable future, a key preventive strategy for women at familial risk for ovarian cancer will continue to be prophylactic oophorectomy. Consistent with the cognitive–social framework, the available literature shows that health-relevant encodings, expectancies, and affect are related to women's decision-making processes. Specifically, patients are more likely to opt for prophylactic oophorectomy when they feel highly vulnerable to cancer [58, 60], perceive that surgery will be effective in preventing cancer [28], and are highly distressed about their cancer risk [65, 66]. This pattern of reactions may undermine informed decision making by prompting individuals to impulsively opt for preventive surgery without fully considering the benefits and limitations of the procedure. However, it should be noted that the associations observed in prior studies have yet to be prospectively examined. Further, the research conducted to date has focused primarily on women's intentions to undergo prophylactic surgery, rather than on women's actual decision-making processes and subsequent behavioral choices. There is also a need for longitudinal studies to explore the correlates and consequences of these relationships over time.

The data reviewed may have implications for the development of counseling protocols. Specifically, patients may need to be helped to take account of the psychological consequences of alternative options for them personally [74]. That is, informed decision making may require that potential candidates be able to realistically process and anticipate the benefits, as well as the limitations, of undergoing preventive surgery [48, 74]. At present, existing guidelines do not deal with how to convey information to patients so as to facilitate decision making and to enhance subsequent adaptation to the scenarios that unfold [74]. Further, the psychological factors that undermine the effective utilization of risk information have not received systematic attention, particularly in the case of healthy women contemplating prophylactic oophorectomy.

Traditionally, counseling programs have focused on improving the comprehension of cancer risk feedback and educating patients about their options [59, 75]. One approach has been to offer personalized cancer risk counseling to women, based on their specific familial, reproductive, and other personal risk factors [e.g., 75, 76]. The results show that women who receive personalized risk feedback are significantly more likely to accurately estimate their risk and to report reductions in cancer-specific distress, compared to women who receive general health feedback [59, 75]. Yet two-thirds of women continue to overestimate their risk for cancer [75]. Hence, merely providing education and information about a medical procedure or test is not sufficient for optimal decision making [77]. Thus, counseling interventions may be needed that explicitly address the cognitive and affective barriers that undermine informed decision making.

The findings also suggest that, in addition to providing personalized risk feedback, counseling interventions may need to be tailored to the individual's psychological profile. Monitors tend to overestimate their vulnerability to cancer [69] and to experience increased levels of disease-related distress and anxiety [69, 72]. Blunters, in contrast, tend to feel less vulnerable to cancer and to manifest lower levels of distress [48, 78]. Specifically, monitors tend to perceive themselves to be more vulnerable to cancer, have more negative expectancies about one's cancer risk status, and experience more distress about their cancer risk compared with their blunting counterparts. Further, findings in other cancer models show that outcomes

are improved when the individual's attentional style is explicitly targeted in intervention communications [69, 79–81]. Future work should more systematically extend research on monitoring–blunting attentional style to decision making about ovarian cancer risk. In particular, there is a need for studies that explore whether monitors benefit from interventions that inform them about the potential limitations of prophylactic oophorectomy and provide support for the complex emotional reactions that may be triggered, and whether blunters benefit from interventions that orient them to the possible advantages of the procedure [69, 80, 82].

The principles that need to be tested and the techniques that need to be developed for informed decision making are not only relevant to the medical and psychological management of ovarian cancer risk, but also may lay the groundwork for cancer prevention counseling protocols for other groups of at-risk individuals [83]. Ultimately, the findings of this type of research should fill a theoretical and empirical gap by providing a framework for specifying how to systematically prepare at-risk individuals for decision making, tailored to the distinctive psychological profile of the patient. This, in turn, should improve a range of patient outcomes, including decision making, satisfaction, quality of life, and adherence over the long-term.

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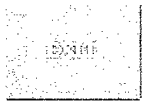
# APPENDIX E

## DATA MANAGEMENT CORE

### Example Electronic Data Entry Screens

# *DOD OV*
# *Main Menu*

| | |
|---|---|
| Health History Survey | BDI |
| Health Care Recommend | RIES Supplement |
| Cancer Risk Perceptions | Ovarian RIES |
| Perceptions of Con and Eff | STAI |
| Beliefs | Ovarian Cancer Knowledge |
| Pros/Cons | Monitoring Attentional Style |
| Short COPE | Interest/Intentions |
| Short POMS | Decision Evaluation |
| Risk & Cancer (Breast) | Risk & Cancer (Ovarian) |



ON-STUDY FORM

Protocol

98-029

Study Number:

Medical Record #:

Name:

SEX: FEMALE

Date of birth:

**Race:**

- White
- Black
- Hispanic
- Asian/Pacific Islander
- Native American
- Other

Missing

Specify

## Baseline PS:

- Fully Active - 0
- Restricted but ambulatory - 1
- Ambulatory and capable of selfcare - 2
- Capable of only limited selfcare - 3
- Completely disabled - 4

## Type of study:

- Full study
- Tissue donation only

Date of Signed Consent (date of enrollment):

Date of 1st Study Drug:

Doctor's Name:

Hospital:

SAVE

Exit

Enter the subject's study id.

Record: 1/1

Insert

# GYN PHYSICAL EXAM

Study ID #: [ ] MR Number:

Date of examination: Month:

| | 1 | 2 | 3 | ? | SPECIFY IF ABNORMAL |
|---|---|---|---|---|---|
| Speculum Exam | | | | | |
| Vaginal cylinder | ⌄ | ⌄ | ⌄ | ^ | |
| Cervix | ⌄ | ⌄ | ⌄ | ^ | |
| Other | ⌄ | ⌄ | ⌄ | ^ | |
| Bi-manual Exam | ⌄ | ⌄ | ⌄ | ^ | |
| Rectovaginal Exam | ⌄ | ⌄ | ⌄ | ^ | |
| External Genitalia | ⌄ | ⌄ | ⌄ | ^ | |
| Inguinal Nodes | ⌄ | ⌄ | ⌄ | ^ | |

Date:

Save

Exit

Enter the Call Number (study id)
Record: 1/1 Insert

# 98-029

# Compliance Measures

Study ID #:

MR #:

| Month | Date Drug Started | Date Drug Ended | # of Pills Patient Should Have Taken | # of Pills Taken | % of Prescribed Pills taken | P= | C= | A= |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |

Save Exit

97-832

# Health History Survey

Study ID #:

1) Have you ever been diagnosed with any form of cancer? Yes No

| Type of cancer | Month | Year | Type of treatment | Still being treated |
|---|---|---|---|---|
| | | | | Yes No Missing |
| | | | | Yes No Missing |
| | | | | Yes No Missing |
| | | | | Yes No Missing |
| | | | | Yes No Missing |
| | | | | Yes No Missing |
| | | | | Yes No Missing |
| | | | | Yes No Missing |

List Values Save Exit

97-832

# Health Care Recommendations

Study ID #:

1. Has a doctor ever given you any recommendations(s) ... Yes No Don't Know Missing

a. If yes, which of the following recommendations(s) were given to you? CLICK TO CHECK

| | | | |
|---|---|---|---|
| Oral contraceptives | | Blood tests | |
| Pelvic Exams | | CA-125 testing | |
| Abdominal Ultrasounds | | Prophylactic Oophorectomy | |
| Transvaginal Ultrasounds | | Referral to a specialist | |

Other

| | Not at all | A little bit | Moderately | Quite | Extremely | Missing |
|---|---|---|---|---|---|---|
| 2. In general, how important are your doctors' recommendations ... | | | | | | |

Save Exit

97-832

# Beliefs About Screening & Risk Reduction

Study ID #:

| | Not at All | Somewhat | Moderately | Very | Completely | No Opinion | Missing |
|---|---|---|---|---|---|---|---|
| 1. Reduce stress | | | | | | | |
| 2. Eat a low fat diet | | | | | | | |
| 3. Take vitamins | | | | | | | |
| 4. Take birth control pills | | | | | | | |
| 5. Childbearing | | | | | | | |
| 6. Prophylactic oophorectomy | | | | | | | |
| 7. Dietarty/herbal supplements | | | | | | | |
| 8. Avoid environment toxins | | | | | | | |
| 9. Alt. therapy - specify | | | | | | | |
| 10. Other - specify | | | | | | | |

**********

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 1. Pelvic examination | | | | | | | |
| 2. Abdominal ultrasound | | | | | | | |
| 3. CA-125 blood test | | | | | | | |
| 4. Transvaginal ultrasound | | | | | | | |
| 5. Other - specify | | | | | | | |

Save Exit

97-832

# RIES Supplement

Study ID #: [ ]

Which of the following statements best describes your beliefs about your cancer risk? (please check one)

- Breast cancer risk is equal to ovarian cancer risk
- Breast cancer risk is greater than ovarian cancer risk
- Ovarian cancer risk is greater than breast cancer risk
- Missing

| | Not at all | Rarely | Sometimes | Often | Missing |
|---|---|---|---|---|---|
| **BREAST CANCER** | | | | | |
| I thought about it when I didn't mean to. | | | | | |
| I avoid letting myself get upset when I thought about it or was reminded of it. | | | | | |
| **OVARIAN CANCER** | | | | | |
| I thought about it when I didn't mean to. | | | | | |
| I avoid letting myself get upset when I thought about it or was reminded of it. | | | | | |

Save Exit

97-832

# Decision Evaluation

Study ID #:

1. Have you made a decision about having a prophylactic ... YES NO Missing

2. When did you make your decision? (month/year) / 

| | Not at all | A little | Somewhat | Very | Extremely | Missing |
|---|---|---|---|---|---|---|
| 3. How satisfied are you with your decision about ... | | | | | | |
| 4. How confident are you that you made the right decision ... | | | | | | |
| 5. How distressed were you while you were making your ... | | | | | | |

6. Have you had the prophylactic oophorectomy surgery? YES NO Missing

   If yes, when (month/year) / 

| | | | | | | |
|---|---|---|---|---|---|---|
| 7. How confident are you that you will make the right ... | | | | | | |
| 8. How distressed (e.g., nevrous, anxious, depressed) ... | | | | | | |

Save Exit

97-832

# Risk and Cancer – Ovarian

Study ID #:

| | Much lower | A little lower | About the same | A little higher | Much higher | NA | Missing |
|---|---|---|---|---|---|---|---|
| 1. In your opinion, compared to other women your own age, ... | | | | | | | |
| 2. In your opinion, compared to other women who have a close ... | | | | | | | |

3. Please rate your chance of getting ovarian cancer someday on a scale from 0 to 100, ...

| | Not at all or Rarely | Sometimes | Often | A lot | NA | Missing |
|---|---|---|---|---|---|---|
| 4. During the past month, ... chances of developing ovarian cancer? | | | | | | |
| 5. During the past month, ... affected your mood? | | | | | | |
| 6. During the past month, ... perform your daily activites? | | | | | | |

Save Exit

# *Have a Name? Find the FRAP ID*

Can use WILDCARD (%) as part of name (i.e. EVER% returns all names beginning with EVER

| First | Middle | Last | BirthDate | Address1 | Address2 | City | State | Zip |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | |

< > Query Exit

Enter a query; press Alt-F11 to execute, Control-F4 to cancel.
Record: 1/1 Enter-Query Insert

97-832

# Old FRAP Participants

Study ID #: [ ] [Tab off field]

Name:

Date of Birth:

Date of Contact: {format as mm/dd/yyyy}

Date of Baseline:

Recruited for Ovarian Behavioral Study: Ref/Acc? If Refused, Why?

List Values Save Exit